

REMARKS

Claims 1-3 and 7-15 are currently pending in the present application. The Office Action is non-final. Claims 3 and 14 are withdrawn from further consideration as being directed to the non-elected species. Claim 1 has been amended. Support for amended claim 1 can be found in the specification on page 17, lines 1-4, page 18, lines 11-19, and Figure 3. Claim 15 is new. Support for new claim 15 can be found in the specification on page 18, lines 25-30, page 19, lines 23-25 and Figure 3. No new matter has been added.

Pending claims 1-2 and 7-15 considered together with the following remarks are believed sufficient to place the application into condition for allowance. Accordingly, an early and favorable action on the merits is earnestly solicited at present.

Rejection under 35 U.S.C. § 112, First Paragraph

Pages 3-5 of outstanding Office Action

Claims 1-2 and 7-13 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

Reconsideration and withdraw of each of the above rejections is respectfully requested based on the following considerations.

New Matter

The Examiner recites:

the amended terms “the mRNA is isolated without removing the cell from the substrate”, “the mRNA transcribed therefrom” and “simultaneous” detection are not supported in the as-filed specification (see Office Action, page 3).

In order to further the prosecution of this application, and without acquiescing to the Examiner's rejection of the claims, these terms have been removed from the pending claims. The terms described above are not necessary to distinguish the invention from the prior art cited.

Therefore, Applicants believe that the present amendment of claim 1 will simplify the issues and advance the prosecution of the application towards allowance.

Written Description

The Examiner states that the specification fails to provide an adequate written description of the invention (*see Office Action, pages 4-5*).

In response to the basis of this rejection, it is noted that the specification discloses a process for identifying and selecting heterologous DNA which causes, in its expression, an electrophysiological change in a cell. In the disclosed process, the heterologous expression level is quantitatively determined using a chip construct as described in Figure 3 to perform patch clamp testing. One skilled in the art could select appropriate cells expressing heterologous DNAs based on a comparative phenotype measurement. The Examiner has not cited any objective evidence to the contrary, such as a reference teaching why selection of cells for expression libraries would require more written description.

The Examiner states that the specification does not provide any particular examples, but discloses that the expression levels can be determined by an analytical method consistent with voltage changes, this type of measurement requires actual physical steps and the specification does not describe every physical or chemical property of the assay. Applicants have amended claim 1 to recite positive, active method steps. Applicants argue that the claimed invention is drawn to a generic method for screening expressed polypeptides for identification and is not directed to the polypeptides products. The novelty of the present invention is focused on the use of a substrate having two surface parts, as claimed.

The Examiner states that the specification does not provide an actual reduction to practice of any specific cells or expression vectors, or identify any specific method of obtaining expression level data for voltage changes, or any specific algorithm for processing the data. However, Applicants remind the Examiner that the level of skill and knowledge in this art is such that those skilled in the art know (1) how to analyze expression levels from a DNA library, (2) methods of expressing one vector within one cell, (3) how to program a computer to accept and display comparative voltage data, and (4) isolate and characterize the mRNA. Applicants

have amended claim 1 to recite positive, active method steps. Case law suggests that the specification need not disclose, and preferably omits, that which is known in the art (*Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986). (MPEP § 2163(II)(A)(2)).

With regards to the method of identifying heterologous DNA, the art is sufficiently developed so as to put one skilled in the art in possession of the complete steps of the process as now claimed.

Based on these factors, those of skill in the art would recognize the inventor to have been in possession of the claimed method at the time of filing. Moreover, the Examiner has not provided any references to prove that the state of this advanced art is such that the specification as filed fails to provide an adequate written description.

Thus, Applicants believe the specification satisfies the written description requirement of 35 U.S.C. § 112, first paragraph with respect to the present claims.

Rejection under 35 U.S.C. § 112, Second Paragraph

Pages 5–7 of outstanding Office Action

Claims 1-2 and 7-13 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (see *Office Action*, page 5-7).

A. The Examiner states:

Claim 1 is being incomplete for omitting essential steps and/or elements, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the steps by which a cell of interest can be identified by its electrophysiological effect by the mere providing of a substrate on a plurality of cells and arranging the plurality of cells on the substrate. It is not clear how the heterologous DNA is expressed such that the cell undergoes electrophysiological changes. Furthermore, it is unclear as to the heterologous DNA and the transcription of mRNA occurring in the cells.

In response to this rejection, Applicants have amended claim 1 to recite additional steps for identifying its electrophysiological effects on said cells. Claim 1 now recites that the substrate comprises a first surface part and an opposite second surface part, wherein a change in the electrophysiology of each cell is measured in a whole cell configuration method of patch-clamping.

However, with regards to the transcription of mRNA occurring in the cells, Applicants contend that expression vectors for heterologous DNA transcription and translation are well known in the art and do not represent essential limitations that must be recited in the claims.

B. The Examiner states:

The claimed a “heterologous DNA sequence” is unclear, within the claimed context, as to the scope of the heterologous DNA sequence in the different plurality of cells especially in the absence of positive definition/support in the specification.

With regards to the term “heterologous DNA”, Applicants have directed the Examiner’s attention to page 11, lines 9-14 of the specification which defines the term.

The DNA sequence introduced to the target cell **is heterologous DNA**, by which **we mean** a DNA sequence that has been introduced to the cell over and above the cell’s normal DNA contents, and wherein each heterologous DNA member of the DNA library differs from each other member by one or more nucleotides.

(reproduced for the Examiner’s convenience, emphasis added)

C. The Examiner states:

“The cell of interest” is unclear as to the basis or standard by which one bases the cell of interest especially in the absence of positive support in the specification.

With regards to the term “The cell of interest”, Applicants argue that the cell and/or genetic material of interest is derived from the heterologous DNA, supported in the specification on page 2, lines 13-14.

Preferably, the **cell and/or genetic material of interest** is isolated to enable further study of the heterologous DNA e.g. by sequencing.

(reproduced for the Examiner's convenience, emphasis added)

D. The Examiner states:

It is unclear as to the “genetic material” the cell of interest that is being referred to. Is this the mRNA or heterologous DNA (See Fig. 2 above, which refers only to mRNA and not genetic material). Thus, there is an inconsistency in what is being claimed.

With regards to the term “genetic material”, Applicants argue that the genetic material is derived from the heterologous DNA, supported in the specification on page 2, lines 13-14 as recited above.

E. The Examiner states:

Claim 2 is unclear as to the positive step required for the “step of sequencing the genetic material” given no genetic material specifically referred thereto. It is suggested that Applicants recite a positive step rather simply the term “step”.

With regards to the term “step of sequencing the genetic material”, Applicants argue that the level of sequencing is so high that additions steps defining the specific process are not required and are clearly known to one skilled in the art. Moreover, claim 2 encompasses all of the limitations of claim 1. Claim 1 recites isolating the genetic material there from. One skilled in the art would understand what steps are required for sequencing the genetic material.

F. The Examiner states:

In claim 7 “each different heterologous DNA sequence is part of a cDNA library” is confusing as to how the DNA sequence is only a part rather than the cDNA library itself i.e., that the DNA is a cDNA library.

With regards to the term “each different heterologous DNA sequence is part of a cDNA library”, Applicants argue that the DNA is accurately described as part of the library. Furthermore, a library is comprised of a collection of cDNA sequences (heterologous DNAs) generated from mRNA (messenger RNA) sequences containing vectors, promoters etc. Therefore, Applicants contend that each heterologous DNA sequence is accurately characterized as part of said library.

G. The Examiner states:

Claim 13 “spaced-apart” locations are indefinite as to how or what the spacing of the cells is such that each is apart from each other. This term is a relative term. It is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

With regards to the term “spaced-apart”, Applicants argue that as shown in Figure 2, a single cell target cell must be positioned in the test site for expression and functional screening. Therefore, for the assay to function the cells must be spaced-apart on the substrate. The Examiner is required to give the "broadest reasonable interpretation" to any claim limitations. Accordingly, the PTO may not disregard the structure disclosed in the specification corresponding to such language when rendering a patentability determination. In the context of the specification and claims, “spaced apart” means that at least two cells are not touching each other.

Rejection under 35 U.S.C. § 102(e)/103(a)

Claims 1-2 and 7-13 stand rejected under 35 U.S.C. § 102(c) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Qin *et al.* (US 6,994,993).

Claims 1-2 and 7-13 stand rejected under 35 U.S.C. § 102(e) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Maher *et al.* (US 6,969,449).

Claims 1-2 stand rejected under 35 U.S.C. § 103(a) as obvious over Qin *et al.* (US 6,994,993) or Maher *et al.* (US 6,969,449), in view of Hutchens *et al.* (US 6,818,411).

Reconsideration and withdrawal of the above rejections are respectfully requested based on the following considerations.

Legal Standard For Anticipation

The standard for a rejection under 35 U.S.C. § 102(b) is established in MPEP §2131. A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. If an independent claim is allowable under 35 U.S.C. § 102, then any claim depending therefrom is also allowable.

Distinctions Over the Cited Art

Qin et al. (US 6,994,993)

In contrast to the present invention, it appears that the specification of Qin *et al.* actually disclose a method of screening for a modulator (compound) of sodium channel activity comprising the steps of co-expressing a protein closely related to a human $\beta 1A$ sodium channel subunit protein and a sodium channel α subunit protein wherein the recombinant cell elicits a sodium ion flux. The present invention requires that the substrate is comprised of a first surface part and an opposite second surface part, wherein the first part has a plurality of sites each of which is adapted to hold an ion channel-containing structure.

Thus, Qin *et al* fail to disclose all the elements in the method steps of the presently claimed invention. That is, it appears that Qin *et al* require co-expression of sodium channel subunit proteins and screening for compounds that either increase or decrease the capacity to

open the sodium channel, whereas Applicants' claims require only a single expression vector in a method of identifying proteins which cause an electrophysiological change in a cell. Additionally, claim 1 of the present invention is not screening for a compound that effects the sodium channel as disclosed by Qin *et al.*

Maher *et al.* (US 6,969,449)

In contrast to the present invention, it appears that the specification of Maher *et al.* (similar to Qin *et al.*) discloses a method of screening for a modulator (compound) of sodium channel activity comprising the steps of selecting cells or clones based on their response to electrical stimulation.

Thus, Maher *et al.* also fail to disclose all the elements in the method steps of the presently claimed invention. That is, it appears that Maher *et al.* require external electrical stimulation for selection of cells or clones, and for the screening methods that measure the effects of test compounds on regulated ion channels.

In contrast, the present invention is drawn a method of identifying proteins which causes or creates an electrophysiological change in a cell and the method of measuring the electrophysiological change is by patch-clamping. The present invention is drawn to patch-clamp detection of a electrophysiological change caused by the expression of the heterologous DNA.

Additionally, claim 1 of the present invention is not screening for a compound that effect the sodium channel as disclosed by Maher *et al.* Neither the Qin *et al.* (US 6,994,993) nor Maher *et al.* (US 6,969,449) reference teach or provide any rationale for the present invention which uses a two surface part substrate.

Therefore, it is submitted that neither the Qin *et al.* (US 6,994,993) nor Maher *et al.* (US 6,969,449) reference teach each and every limitation of the present claimed invention.

Accordingly, the present invention is not anticipated by either the Qin *et al.* (US 6,994,993) or Maher *et al.* (US 6,969,449) references of record. Any contention of the USPTO to the contrary must be reconsidered at present.

Legal Standard for Determining Prima Facie Obviousness

M.P.E.P. § 2143 sets forth the guidelines in determining obviousness. First, the Examiner has to take into account the factual inquiries set forth in *Graham v. John Deere*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), which has provided the controlling framework for an obviousness analysis. The four *Graham* factors of: determining the scope and content of the prior art; ascertaining the differences between the prior art and the claims that are at issue; resolving the level of ordinary skill in the pertinent art; and evaluating any evidence of secondary considerations (e.g., commercial success; unexpected results). 383 U.S. 1, 17, 148 USPQ 459, 467 (1966). Second, the Examiner has to provide some rationale for determining obviousness, wherein M.P.E.P. § 2143 set forth some rationales that were set established in the recent decision of *KSR International Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007). Here, the Examiner has not appropriately resolved the *Graham* factors, including ascertaining the differences between the prior art and the claims that are at issue, and the rationale in combining the cited references is improper.

The rationale should be made explicit, *KSR International Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), and the Examiner must interpret the reference as a whole and cannot pick and choose only those selective portions of the reference which support the Examiner's position. *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.").

Applicants contend that the arguments described above with respect to distinctions over the teachings and disclosures of the cited *Qin et al.* (US 6,994,993) or *Maher et al.* (US 6,969,449) references are equally applicable here (and are incorporated herein by reference in their entirety).

As the M.P.E.P. directs, all claim limitations must be considered in view of the cited prior art in order to establish a *prima facie* case of obviousness. *See* MPEP § 2143.03.

MPEP § 2143.03 recites examples of Basic Requirements of a *Prima Facie* Case of Obviousness and seven exemplary rationales.

Note that the list of rationales provided is not intended to be an all-inclusive list. Other rationales to support a conclusion of obviousness may be relied upon by Office personnel.

However, Applicants fully address these rationales below. According to Applicants analysis below, the Examiner has not met the basic requirements of a *prima facie* case of obviousness. More specifically, Applicants contend that:

- (A) Combining prior art elements according to known methods cited do not yield predictable results yielding a method for identifying heterologous DNA expression causing a electrophysiological change in a cell, measured by a whole cell configuration method of patch-clamping on the substrate comprising a first surface part and an opposite second surface part, wherein the first part has a plurality of sites each of which is adapted to hold an ion channel-containing structure;
- (B) Simple substitution of one known element, a substrate for detecting electrophysiological change in a cell using only one side of a substrate, does not yield predictable results in regards to the use of a substrate comprising a first surface part and an opposite second surface part;
- (C) There is no known technique to improve a electrophysiological change in a cell by using a substrate comprising a first surface part and an opposite second surface part as claimed;
- (D) Applying a known technique as taught Qin *et al.* or Maher *et al.* does not yield predictable results for said detection using a substrate comprising a first surface part and an opposite second surface part as claimed;
- (E) The Examiner cannot support the conclusion of "obviousness" on the basis "Obvious to try" – there are no predictable methods or models cited by the Examiner that establish a reasonable expectation of success for the detection method using a two surface part substrate;
- (F) There is no reason or rationale cited by the Examiner that may prompt variations from the disclosure of Qin *et al.* or Maher *et al* that would result in the claimed expression method of identifying heterologous DNA by using a two surface part substrate;

(G) There is no teaching, suggestion, or motivation in the prior art cited by the Examiner that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed expression method of identifying heterologous DNA by using a two surface part substrate.

Hutchens *et al.* (US 6,818,411)

Hutchens *et al.* disclose methods of analyzing complex mixtures for physiological properties in an array format. Hutchens *et al.* do not disclose patch-clamp methods, current clamp, or any other techniques comprising electrophysiological potential analysis.

Therefore, the secondary cited art of Hutchens *et al.* (US 6,818,411) is incapable of curing the above noted deficiencies of either Qin *et al.* (US 6,994,993) or Maher *et al.* (US 6,969,449), and thus is incapable of rendering the instant invention as claimed obvious.

It is submitted that the claimed method allows the identification of DNA being expressed in a cell in direct correlation with electrophysiological effects of that DNA, which cannot be achieved by the methods of the prior art cited. The DNA in the present invention can be any sequence and does not have to encode a known protein that relate to electrophysiological aspects (e.g. a sodium channel).

Accordingly, the present invention is not rendered obvious in view of the teachings and disclosures of the cited Qin *et al.* (US 6,994,993) or Maher *et al.* (US 6,969,449) references and/or the cited Hutchens *et al.* reference of record. Any contentions of the USPTO to the contrary must be reconsidered at present.

CONCLUSION

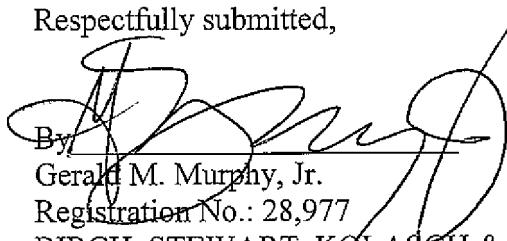
In view of the above amendments, Applicants believe the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Eggerton A. Campbell, Reg. No. 51,307, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.147; particularly, extension of time fees.

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Respectfully submitted,


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